

Docket No.: ISIS-5325

Application No.: 10/701,007

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
Charles Allerson, et al.

Confirmation No.: **5641**

Application No.: **10/701,007**

Group Art Unit: **1635**

Filing Date: **November 4, 2003**

Examiner: **Jane J. Zara**

For: **Compositions Comprising Alternating 2'-Modified Nucleosides For Use In Gene Modulation**

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

APPELLANT'S REPLY BRIEF PURSUANT TO 37 C.F.R. § 41.41

Appellants submit this reply brief in response to the Examiner's answer issued July 19, 2010 in connection with the above-identified patent application. This reply brief is being filed within two months of the Examiner's answer.

ARGUMENT**The Examiner's Answer Fails to Demonstrate that the Claimed Compositions Would Have Been Obvious**

It remains undisputed that the combined teachings of the Elbashir, Giese, Fosnaugh, Morrissey, Arnold, Damha, and McKay references, in view of the state of the art at the time of the invention, fail to teach the claimed compositions comprising certain specifically modified oligomeric compounds. Further, it remains undisputed that those references fail to create a reasonable expectation that specific oligomeric compounds would be successful for RNA interference, due to the high degree of unpredictability in the art at that time. Accordingly, the Examiner has failed to establish that the claimed oligomeric compounds would have been obvious before appellants' invention.

Nothing in the cited art would have provided a reasonable basis for predicting that the particular oligomeric compounds claimed would have been active siRNAs. The cited references themselves describe a virtually *limitless* number of possible patterns and combinations of chemical modifications that could have been incorporated into siRNA molecules. However, they describe the actual production and testing of only *a very limited number* of chemically modified siRNA molecules. The references thus provide extremely limited information regarding the effects that different types and combinations of chemical modifications have on the properties and biological activities of siRNAs.

Rather than establishing that the cited art would have provided a reasonable basis for predicting that the claimed compounds would have been successful, the Examiner instead alleges that the art provides "a reasonable expectation of success of *finding* the instantly claimed design choice of modified oligonucleotides."¹ Indeed, throughout prosecution, the Examiner based the alleged obviousness of the claimed compounds on the supposed routine nature of generating and testing candidate compounds generally. For example, at page 18 of the Examiner's Answer, the Examiner remarks that, "[i]t merely requires the systematic testing of the modifications' effects

¹ Examiner's Answer at page 20 (emphasis added).

on siRNA activity.”² And in the paragraph spanning pages 10 to 11 of the answer, the Examiner remarks that “[o]ne of ordinary skill in the art would have produced various motifs as a matter of design choice . . . after testing various modifications and their combinations” Contrary to the Examiner’s assertions, the availability of methods that might have been used to synthesize and screen some of the vast number of possible unpredictable candidate compounds would not have been sufficient to render obvious the claimed oligomeric compounds having specific arrangements of particular modifications.³ Moreover, since the Examiner provides no credible reason that would have prompted one of ordinary skill in the art to select the particular molecules claimed, and no reason that one of ordinary skill in the art would have expected them to be active, the present rejection could just as easily be applied to every one of an infinite number of oligomeric compounds having unpredictable combinations of modifications. In other words, according to the Examiner’s reasoning, the existence of routine screening assays renders *all chemically modified oligomeric compounds* obvious. Such a result is inconsistent with the tenants of patent law and is contrary to precedent.

In this regard, the Supreme Court has held that claimed subject matter is obvious if it could have been arrived at by simply choosing from among a *finite* number of identified, *predictable* solutions, with a *reasonable expectation of success*.⁴ That certainly does not describe the circumstance in the present case, which instead involves a virtually infinite number of modifications and combinations of modifications in an unpredictable art. This unpredictability in the art at the time of the present invention mirrors the circumstances at issue in *Takeda Chemical Industries, LTD v. Alphapharm Pty, Ltd.*⁵ As discussed during prosecution, in *Takeda* the Federal Circuit determined that a new chemical compound produced via routine modification of an existing compound was non-obvious because, despite the routine nature of the

² Examiner’s Answer page 12; see also, e.g., pages 9 to 10 (bridging paragraph), pages 10 to 11 (bridging paragraph); page 16, (full paragraph).

³ *Takeda Chemical Industries, LTD v. Alphapharm Pty, Ltd.*, 492 F.3d 1350, 1356 (Fed. Cir. 2007).

⁴ M.P.E.P. § 2143 E, citing *KSR Int’l Co. v. Teleflex*, 127 S.Ct. 1727, (2007).

⁵ *Takeda Chemical Industries, LTD v. Alphapharm Pty, Ltd.*, 492 F.3d 1350, 1356 (Fed. Cir. 2007) (emphasis added), discussed at length in the response filed June 24, 2009.

rather simple chemical modifications used to produce the new compound, the effects of the modifications on the compound's activity and properties were unpredictable.

Moreover, as the updated examination guidelines recently published by the USPTO explicitly state, “[i]f results would not have been predictable, Office personnel should not enter an obviousness rejection using the combination of prior art elements rationale, and should withdraw such a rejection if it has been made.”⁶ The guidelines also remark that even “where there was reason to select and modify the lead compound to obtain the claimed compound, but no reasonable expectation of success, the claimed compound would not have been obvious.”⁷

The holdings of cases such as *Takeda*, *Ortho McNeil*, and *Proctor and Gamble* are applicable to the present application due to the high degree of unpredictability in the art at the time of the invention. The Examiner erred in determining that the allegedly routine nature of producing and testing candidate chemically modified oligomeric compounds would have rendered the claimed compounds *prima facie* obvious. Thus, the Examiner's conclusion of obviousness constitutes legal error.

⁶ Examination Guidelines Update: Developments in the Obviousness Inquiry After *KSR v. Teleflex*, Fed. Reg., Vol. 75, No. 169 (2010) at 53647 (discussing *Crocks, Inc., v. US International Trade Commission*).

⁷ *Id.* at 53652 (discussing *Proctor & Gamble Co. v. Teva Pharm.*)

Conclusion

For the reasons set forth above, the Examiner's rejection for alleged obviousness is in error and should be reversed. Appellants accordingly request that the present patent application be remanded to the Examiner with an instruction to withdraw the rejection.

Respectfully submitted,

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